

## REMARKS

### Status of the Claims

Claims 1-23 were originally pending in the application. Claims 1-2 and 19-23 were previously canceled. Claims 3-18 have been rejected. Claim 17 has now been canceled. Claims 3-16 and 18 are now pending. Reexamination and reconsideration of the claims are respectfully requested.

### The Rejection Under 35 U.S.C. §112 Second Paragraph Should be Withdrawn

Claim 17 remains rejected by the Examiner under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly pointing out and distinctly claiming the subject matter which the Applicant regards as the invention. In particular, the Examiner argues that the term “DNA chelating agent” is unclear. The Applicant disagrees. As pointed out in the Applicant’s previous response of April 25, 2006, since the term “DNA chelating agent” is well known to one skilled in the art, including the Examiner, the Applicant does not need to define the term, either in the claims or the specification. However, in order to expedite prosecution, the Applicant proposes to cancel claim 17 without prejudice. Applicants also reserve the right to pursue the restricted subject matter in a later application. Applicant respectfully requests that the rejection to claim 17 under 35 U.S.C. §112 second paragraph be withdrawn.

### The Rejections Under 35 U.S.C. §103(a) Should be Withdrawn

Claims 3-18 remain rejected by the Examiner under 35 U.S.C. 103 as being unpatentable over Richards (USP 5,645,987) in view of U.S. Patent No. 5,230,350 to Kurn and in further view of U.S. Patent No. 5,916,777 to Kacian. The Applicant traverses this rejection.

With regard to the rejection as it applies to claims 3 and 10, the examiner states that: “It would have been *prima facie* obvious to one of skill in the art at the time that the time the invention of the instant application was made to incorporate the chimeric primers and RNase H digestion taught by Kacian and the ‘blocker’ oligonucleotides taught by Kurn in the ‘primer extension cascade’ taught by Richards.” The Applicant once again respectfully disagrees.

The Applicant submits that Richards neither anticipates the claims nor are they made obvious by either Kurn or Kacian. The Examiner responds to the Applicant's argument by stating that one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. Although the Applicant agrees that one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references, the Applicant also would point out that the Examiner, in order to establish *prima facie* obviousness of a claim, must demonstrate that all of the limitations of the claim must be taught or suggested by the prior art. In re Royka 490 F.2d 981 (CCPA 1974). Therefore, if the Applicant can demonstrate that all the limitations of the present claims cannot be found in Richards alone or in combination with Kurn or Kacian, then the Examiner has not established *prima facie* obviousness.

As previously stated by the Applicant, Richards does not teach or suggest the claims of the present invention. The Examiner argues that Richards teaches a method comprising a primer extension cascade in which the cleaved and released primer extension product from a first primer extension reaction serves as a primer in a subsequent primer extension reactions (as depicted in Figure 6). The Examiner then points out the claim limitations that Richards does not teach such as a chimeric primer, blocking oligonucleotides, thermocycling, RNase to digest the primer extension products or the use of a DNA polymerase which lacks 5' exonuclease activity. The Applicant would respectfully argue that the Examiner has missed at least one very important limitation in the method of the present invention that is not taught in Richards nor Kurn or Kacian. In particular, the Applicant would point to section (c) which is identical in both independent claims 3 and 10. Section (c) reads as follows:

- c.) hybridizing said first primer extension product to a first DNA triggering template comprising a target sequence, a first primer extension product binding site at the 3' terminus of said target sequence, and a contiguous second primer sequence which is conjoined to the 5' end of said target sequence by a ribonucleotide base; (emphasis added)

As described in Claim 3 and demonstrated in Figure 1 of the Applicant's application, the method of the present invention is a multi step process which results in the amplification of a

target sequence (or triggering template). Unlike the process described in Richards, the method of the present invention does not cleave oligonucleotides from extension products which are then used for future rounds of amplification. As shown in Figure 1, the second primer extension product formed by the extension of the first primer extension product is cleaved at the ribonucleotide base at the 5' end of the first DNA triggering template. Thus, the second primer extension product is formed by the cleavage by RNase H at a ribonucleotide base at the 5' end of the target sequence, not the primer extension product as shown in Richards. Also, the method of the present invention includes the extension of a second DNA triggering template by the second primer extension product created by the cleavage of the first DNA triggering template. The Applicant would once again call attention to the fact that the two DNA triggering templates are distinct from the original DNA sequence from which the first extension product is created. In particular, the first DNA triggering template contains an internal ribonucleotide base which can be cleaved by RNaseH. There is no teaching or suggestion in Richards, Kurn or Kacian of the use of a second DNA target sequence which contains an internal ribonucleotide base for the creation of primer oligonucleotides. The Examiner has not pointed to any teaching in Richards, Kurn or Kacian where two distinct templates that are different in composition than the original DNA template which generates the first primer extension product are used in an amplification process

Because Richards does not recite the creation of an oligonucleotide primer via the cleavage by RNase H at a 5' end of a target sequence or the extension of a second DNA triggering template by the second primer extension product created by the cleavage of the first DNA triggering template, it cannot anticipate all the elements of the claimed invention.

Combining the Richards patent with the Kurn patent and the Kacian patent cannot make up for the deficiencies mentioned above in regards to the Richards patent with respect to the presented claimed invention. Neither the Kurn patent or the Kacian patent teach or suggest a method for amplifying DNA by the creation of an oligonucleotide primer via the cleavage by RNase H at a 5' end of a target sequence or the extension of a second DNA triggering template by the second primer extension product created by the cleavage of the first DNA triggering template.

Lastly, assuming *arguendo* that all the limitations of the present claims can be found in Richards, Kurn and Kacian, the Examiner has not provided the clear, particular suggestion in the art for making the specific claimed combination of Richards, Kurn and Kacian. *Prima facie* obviousness has not been established under such conditions.

A new combination of elements can be patented "whether it be composed of elements all new, partly new or all old." *Rosmount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1546, 221 USPQ 1, 7 (CAFC 1984). The Court of Appeals for the Federal Circuit has forcefully stated that a claim rejection must provide a specific motivation in the art for combining elements from cited art in order to establish obviousness of a new combination.

"[C]ase law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. ... Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. ... [Evidence of a suggestion, teaching, or motivation to combine] must be clear and particular. ... Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.' ... [A] reference-by-reference, limitation-by-limitation analysis fails to demonstrate how the [cited] references teach or suggest their combination ... to yield the claimed invention," and a conclusion of obviousness based on such an analysis "as a matter of law, cannot stand." *In re Dembiczak*, 175 F.3d 994, 999, 1000, 50 USPQ2d 1614, 1617, 1618 (Fed. Cir. 1999), emphasis added.

*Dembiczak* involved patent claims to "a large trash bag made of orange plastic and decorated with lines and facial features, allowing the bag, when filled with trash or leaves, to resemble a Halloween-style pumpkin, or jack-o'-lantern." *Dembiczak*, 996, 1616. The prior art cited by the Board included: a book describing how to teach children to make a "Crepe Paper Jack-O-Lantern;" a book describing a method of making a "paper bag pumpkin" by stuffing a bag with newspapers, painting it orange, and then painting on facial features with black paint; a U.S. Patent describing a bag apparatus wherein the bag closure is accomplished by the use of folds or gussets in the bag material; design patents issued to *Dembiczak*; and prior art "conventional" plastic lawn or trash bags. The Federal Circuit held that the claimed pumpkin-style trash bag was not obvious because there was no clear, particular motivation to combine the cited references.

This holding of *Dembiczak* that evidence of motivation to combine must be clear and particular to establish obviousness has been emphasized over and over again by the Federal Circuit since *Dembiczak* was decided. It was strongly reemphasized in *Ruiz v. A.B. Chance Co.*, 57 USPQ2d 1161 (Fed. Cir. 2000):

In order to prevent a hindsight-based obviousness analysis, we have clearly established that the relevant inquiry for determining the scope and content of the prior art is whether there is a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references. See, e.g., In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("[T]he Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."); In re Dembiczak, 175 F.3d at 999, 50 USPQ2d at 1617 ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."). "Determining whether there is a suggestion or motivation to modify a prior art reference is one aspect of determining the scope and content of the prior art, a fact question subsidiary to the ultimate conclusion of obviousness." Sibia Neurosciences, Inc. v. Cadus Pharma. Corp., 225 F.3d 1349, 1356, 55 USPQ2d 1927, 1931 (Fed. Cir. 2000); Tec Air, Inc. v. Denso Mfg., Inc., 192 F.3d 1353, 1359, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999) (stating that the factual underpinnings of obviousness include whether a reference provides a motivation to combine its teachings with those of another reference).

... there is "a general rule that combination claims can consist of combinations of old elements as well as new elements," Clearstream Wastewater Sys. v. Hydro-Action, Inc., 206 F.3d 1440, 1446, 54 USPQ2d 1185, 1189-90 (Fed. Cir. 2000), "[t]he notion . . . that combination claims can be declared invalid merely upon finding similar elements in separate prior patents would necessarily destroy virtually all patents and cannot be the law under the statute, § 103." Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1575, 1 USPQ2d 1593, 1603 (Fed. Cir. 1987); Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957, 43 USPQ2d 1294, 1297 (Fed. Cir. 1997) ("It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements."). *Ruiz* at 1167

The motivation cited in the Office Action for the proposed combination is as follows:

"It would have been *prima facie* obvious to one of skill in the art at the time the invention of the instant application was made to incorporate the chimeric primers and RNase H digestion taught by Kacian and the "blocker" oligonucleotides taught by Kurn in to the 'primer extension cascade' taught by Richards". (Office Action at page 6, second paragraph).

This statement does not provide the clear, particular suggestion in the art for making the specific claimed combination as is required under *In re Dembiczak*. The claims here are no more obvious than those at issue in *Dembiczak*. No clear, particular suggestion or motivation in the prior art to make the specific method for amplifying a target nucleic acid sequence comprising the steps of;

- a) forming a nucleotide amplification reaction mixture comprising a DNA template containing a target nucleic acid sequence; a single chimeric oligonucleotide primer consisting of a deoxyribonucleotide sequence with a ribonucleotide base at the 3' terminus that binds to said DNA template; a non-extendable oligonucleotide blocker that binds to said DNA template downstream from said primer; a DNA polymerase which lacks 5' exonuclease activity; and a double-strand-specific ribonuclease, and appropriate buffers and nucleic acid precursors;
- b) subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a first primer extension product is formed and cleaved at the ribonucleotide base releasing said first primer extension product;
- c) hybridizing said first primer extension product to a first DNA triggering template comprising a target sequence, a first primer extension product binding site at the 3' terminus of said target sequence, and a contiguous second primer sequence which is conjoined to the 5' end of said target sequence by a ribonucleotide base;
- d) subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a target amplification product is formed and said first DNA triggering template is cleaved at the ribonucleotide base releasing said second primer sequence with a ribonucleotide base at the 3' terminus;
- e) hybridizing said second primer sequence to a second DNA triggering template which contains a second primer sequence binding site at the 3' terminus; and
- f) subjecting said nucleotide amplification reaction mixture to at least one thermocycle such that a third primer extension product is formed and cleaved at the ribonucleotide base releasing said third primer extension product, wherein said third primer extension product has the same nucleotide sequence as the first primer extension product."

as recited in both claims 3 and 10 and much less for the claims dependent thereon with

their additional limitations. The obviousness rejection is based on hindsight from disparate references to provide random elements of the claims. There is no clear, particular motivation in the references to reach the claimed invention. Withdrawal of this rejection under 35 USC 103(a) is respectfully requested.

The Examiner also argues that "...the "primer extension cascade" taught by Richards is so similar to the method claimed in the instant application as to render the latter obvious because the essential differences between the methods taught by Richards and those of the instant application are that Richards uses the primer extension to create a substrate for restriction endonuclease cleavage, while the Applicant uses the primer extension to create a substrate for RNase H cleavage". (see page 6 first paragraph). The Applicant would argue that just because the methodologies are similar does not make them obvious. There are many different types of polymerase chain reaction amplification methodologies (e.g., Inverse PCR; RT-PCR; Asymmetric PCR; Quantitative PCR; Touchdown PCR; RACE-PCR; Multiplex-PCR; etc.) however, it is difficult to imagine that one of skill in the art would agree that all of these methods are obvious in light of the original discovery of the polymerase chain reaction. To argue that two methodologies are obvious because they are similar ignores the many complexities of protocols in molecular biology. Very small changes in methods can result in very dramatic changes in the outcome of those methods. In the present case, the differences between the methodology of Richards as compared to the method of the present invention are more than small changes in protocol. The use of completely different templates for amplification simply cannot be considered an insignificant difference. In fact, the Applicant would argue that using completely different templates makes the methodologies fundamentally different and unique from one another. The cleavage of the template to generate an extension primer is yet another example of one of many differences between the methodology of Richards and the methodology of the present invention. As such, *prima facie* obviousness has not been established under such conditions.

In view of the foregoing, the Applicant respectfully submits that Richards, Kurn and Kacian either alone or in combination, fail to teach or suggest the method of amplifying DNA as

recited in the claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 3-16, and 18.

### CONCLUSION

In light of the amendments and arguments presented above, Applicants respectfully submit that the claims are in condition for allowance. Early notice to this effect is solicited.

In addition, all amendments set forth above would raise no new issues that would require further consideration and/or search. Applicant submits that these amendments would place the claims into condition for allowance, or at least present the rejected claims in better form for consideration on appeal, and should therefore be entered after the final rejection under 37 C.F.R. 1.116 (a).

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 502855 referencing attorney docket number 11.036011.

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